CIGUATERA: DILEMMAS IN CLINICAL RECOGNITION, PRESENTATION AND MANAGEMENT

JOHN PEARN

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Both the clinician and consulting scientist are confronted with several key problems in the recognition and management of the ciguatoxic victim. Failure to consider the possibility of ciguatera in a patient presenting with any one or more of the pleomorphic constellation of symptoms and signs which are the hallmark of the disease, remains the most important ongoing dilemma of management. A differential diagnosis involves 'formulation of a list of diseases, commensurate with the elicited history and the observed signs, arranged in decreasing order of likelihood'. In mild single cases the difficulty of raising a differential diagnosis is compounded by lack of some symptoms. Another dilemma is interpretation of the chronicity of symptoms and this remains a clinical research challenge. A further dilemma is use of Mannitol and timing its introduction. Clinical research shows that Mannitol is not effective if administered more than 48 hrs after symptoms appear.

John Pearn, Department of Child Health, University of Queensland, Royal Children's Hospital, Brisbane, Queensland 4029; 10th May, 1994.

The pleomorphic nature of ciguatera, the subjectivity of many of its symptoms and the absence of any definitive laboratory diagnosis for clinical cases make this condition one of the most challenging in clinical medicine.

The research dilemmas of ciguatoxin classification, source, assay and lesion pathogenesis are paralleled by clinical dilemmas of diagnosis, symptom interpretation and management. In the evolution of the understanding of any human disease there exists a 'window of time' in which one has to make the best of all available clinical experience, however anecdotal and however imperfect, in the practical management of an individual victim. In the case of ciguatera we are hopefully nearing the end of this era of clinical empiricism. Recent identification of the molecular structure of several of the ciguatoxins (Murata et al,1990), advances in understanding of sodium channel pathophysiology (Benoit et al.,1986; Lombet et al.,1987) and unequivocal histological evidence of nerve and muscle changes all contribute to the better interpretation of the miscellany of symptoms and signs which is the hallmark of this 'treacherous and increasingly-occurring marine fish public health hazard' (Russel & Egan,1991).

Many clinical dilemmas remain. These uncertainties are perplexing for the physician but like all dilemmas their resolution will advance the understanding of this enigmatic, common and important disease.

DIFFERENTIAL DIAGNOSIS

Diagnosis of ciguatera is essentially clinical. Currently, it is the failure to consider the possibility of ciguatera, in a patient presenting with any one or more of the pleomorphic constellation of symptoms and signs which are the hallmark of this disease, which remains the most important ongoing dilemma of management. This fact, the overlooking of the possibility of ciguatera rather than any omission of documenting the symptoms and signs remains the major problem in the management particularly of sporadic cases.

One dilemma is that there is no published work on the proportion of sporadic versus multiple cases in any published case series. Although the clinical syndrome is now very well defined (Gillespie et al.,1986) the syndrome boundaries for subacute and chronic cases still remains uncertain. The 'gold standard' of the chronic ciguatera syndrome must include case studies of multiplex (or epidemic) cases, followed prospectively.

The concept of differential diagnosis is 'the formulation of a list of diseases, consistent with the elicited history and the observed signs, arranged in decreasing order of likelihood'. All familiar with ciguatera are aware of the multiplicity of other different diagnoses which are included in the list of possibilities generated by the perplexed victim and his or her family, by the attending first aider, or by the admitting doctor in the emergency room of the referral hospital

Differential diagnosis, in sporadic cases, includes such conditions as viral and bacterial enterocolitis, viraemias of diverse types, some types of hypersensitivity reaction, poisoning with other organic and inorganic agents and various types of neuroses.

Bacterial and viral gastroenteritis can be accompanied by prostration, rash, arthralgia and myalgia and bradycardia. Viral infections can cause puzzling constellations of symptoms and signs including rashes, arthralgia and myalgia, gastro-intestinal disturbances and neurogenic paraesthesiae. In the past, patients with undoubted ciguatera have been labelled as suffering from chronic viral diseases, auto-immune disease, possible insecticide and heavy metal poisoning, psychosis and neurosis, hysteria and malingering.

Subacute and chronic cases, or cases presenting for the first time after several days of symptoms, are always difficult to diagnose. A particular difficulty is the fact that loss of energy, loss of appetite and subjective feelings of weakness are very common indeed in the general population.

The differential diagnosis of ciguatera is always a two-stage process. The first stage is to deduce that one of the icthyosarcotoxaemias is present; the second is to run through the other possibilities of puffer fish poisoning (fugu), maitotoxaemia, clupeotoxism and histamine poisoning. This latter condition, due to histamine poisoning, occurs especially after the ingestion of spoiled *Pomatomus*, or common 'tailor' fish of eastern Australia; and occasionally after the ingestion of *Arripis* or 'Western Australian salmon' (Smart, 1992). The differential diagnosis of the icthyosarcotoxaemias also includes the various forms of diarrhoeal and paralytic shellfish poisoning, especially after the ingestion of mixed seafood meals which include both potentially toxic species such as coral trout (*Plectropomus maculata*) and mackerel (*Scomberomorus commersoni*) together with oysters and scallops.

The author has encountered several cases presenting first following rechallenge with ciguatoxic food one case involving the ingestion of battery-fed chicken, in which the poultry was probably fed on fish meal. In this type of case the diagnosis of the putative original ciguatoxic intoxication can only be made in retrospect.

CHRONICITY OF CIGUATERA

One of the main clinical dilemmas is interpreting the true significant of chronic symptoms. How long can ciguatera last? Most experienced workers have followed cases prospectively and know that objective signs of poisoning usually persist for a few days or several weeks only; yet all know that the subjective, often distressing symptoms such as prostration, arthralgia and myalgia and disordered cutaneous sensation can persist in an unbroken continuum of such subjective symptoms for many months. Can ciguatera produce symptoms, say, after two or three years? At this stage of scientific knowledge there are numerous anecdotal case reports, but doubt persists about the true persistence of symptoms for more than one year or so. At this point of scientific endeavour, no cumulative frequency histograms have been generated, by symptoms, for proven cases followed prospectively. Thus, the chronicity of ciguatera remains an important clinical research issue for the future.

Recent neurophysiological experiments have indicated that the toxin is acting at its affector sites, in organ-bath preparations in fractions of nanomolar concentrations. This fact, combined with its fastness in some neurophysiological experiments lends plausible support to the concept that true symptoms may persist for years rather than months. The principal target of ciguatoxin is on unmyelinated fibres. It is not implausible that one of the most toxic substances known to science (ciguatoxin), and one of such demonstrated strong attachment to its receptor site in the sodium channel, might produce bizarre autonomic-related symptoms for very long periods after the initial insult. Permanent damage to nerves, or residual binding of the toxin to its target receptors, may help explain the often observed phenomenon of recrudescence of symptoms, even in the face of an otherwise subclinical dose of toxin.

INDIVIDUAL SUSCEPTIBILITY

There is considerable individual clinical susceptibility to ciguatoxin. Not infrequently, different family members eating the same toxic fish, and often apparently in similar amounts, are affected to different degrees. The mass of toxic fish eaten is obviously important; and in the case of *very* toxic fish even small differences in plate portions may be reflected in large differences in the mass of toxin which is ingested. Experience in Japan with fugu fish poisoning is that the eating of very large portions of otherwise relatively safe fish has resulted in fatalities (Matsubara, 1981).

Such cases highlight particularly the importance of portion size - and conversely, the need for prudence in the face of potentially risky meals.

Personal clinical experience with managing multiple affected victims who have eaten from the one ciguatoxic fish suggests that individual clinical variation is the rule, rather than the exception. All experienced workers have encountered situations where some members may be totally unaffected following the ingestion of a ciguatoxic fish meal, whilst others eating portions of similar size may be severely affected. Research biologists undertaking the mouse assay for ciguatoxin, also encountered this in a situation where pairs of mice were being used in the biological assay. Not infrequently one member of the pair will be dead within 1-3 hours and the other (although usually affected) will survive. These 'mouse-splits' so often parallel the clinical discordance one sees among the human victims of mini-epidemics.

The basis for this variable susceptibility remains unknown. A significant genetic component is likely although, even within affected families (in family outbreaks), there is not infrequently widespread variation in the severity of symptoms and objective signs. Different species react differently to the toxin, both in terms of quantitative response as crude evidence of poisoning on the one hand, and in qualitative syndromic variation on the other. The 'straub tail' seen in poisoned mice is quite different from the syndrome seen in the (more sensitive) afflicted cat, often used as the practical test animal in real life domestic situations where a family is wishing to consume a risky species of fish.

Some believe that children are particularly susceptible and certainly in various LD_{50} assays for other toxins, neonatal mice are more sensitive than the standard 19–21 gram adults which are more traditionally used in the specific ciguatoxic mouse assay. I have encountered clusters of family poisonings where children appear to be more severely affected. The dilemma remains however that children so often ingest more of the fish, and in a particularly toxic fish meal a relatively small increase in ingested mass (in relation to a child's body weight) may result in a supra-threshold level of ingested toxin. Similarly, sex differences in responses to the toxin are often hinted at, anecdotally in the case of women whom it is thought may be particularly susceptible to the long term effects. No formal attempts at initial dose quantification, with long term follow up by sex, have been reported.

GEOGRAPHIC VARIATION SYMPTOMATOLOGY

Confusion exists about the relative incidence of different symptoms in different parts of the world. Whilst all case series report such things as circum-oral tingling, diarrhoea and vomiting, other symptoms such as dysuria (Gillespie et al., 1986), dental pain, pruritus and piloerection are reported much more frequently in certain geographic regions than in others. Some differences are undoubtedly due to sampling errors, differences in case descriptions and different standards of history taking and of reporting. However, there are obviously different toxins and different toxin subtypes in different areas. Indeed, it seems inescapable that the human clinical syndrome of ciguatera is the result of ingestion of a cocktail of different ciguatoxins. *A priori*, it would be unrealistic not to expect different clinical syndromes under these circumstances, in different parts of the world. There is some evidence that antibody profiles to toxins from fish taken from different parts of the world differ in their cross-reactivity. This gives further credence to the belief that there are subtle differences in ciguatera syndromes in different parts of the world. Nevertheless, in all reported series, a profile of core symptoms is seen and includes gastrointestinal symptoms, neurological complications such as paraesthesiae and temperature dysaesthesiae, myalgia and arthralgia. This also reflects different case definitions which are used.

The role of mannitol therapy (Palafox et al., 1988; Pearn et al.,1989) remains indeterminate, although the necessary double-blind study (from the Marshall Islands) is in progress. In the writer's experience, administration of intravenous mannitol in a dose of 1g/kg body weight, given as an oedema-reducing regimen over a maximum administration time of 45 minutes, produces dramatic alleviation of symptoms within 2–3 hours in some patients. The role of mannitol therapy in cases presenting to medical attention after this time remains controversial and this dilemma will not be resolved until treated cases are followed prospectively. I give mannitol, in cases presenting acutely even although the symptoms may be milder, in the anticipated belief that the risk of long term sequelae will be reduced. What has been established is that mannitol given to the ciguatera patients is safe, and that no synergism between toxin and mannitol has been observed.

To the clinician practising in high-risk endemic regions of the tropical littoral, multiple-case out-

breaks pose no problem in diagnosis and with the advent of mannitol therapy management is much more straightforward. The major problem in the clinical management of ciguatera remains in the need for more widespread awareness of the possibility of the disease, and earlier diagnosis. To the first aider, nurse or physician encountering (particularly sporadic) cases, often distant in place and sometimes distant in time from the fish source, missed diagnosis still remains the biggest challenge in the management of this important disease.

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